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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,978	08/26/1999	HEINZ SCHALLER	BBI-102CP	7239

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	22

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/383,978	SCHALLER ET AL.	
	Examin r	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,33-36,39 and 42-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,33-36,39 and 42-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed on 6/16/03 has been entered as Paper No. 21.

It is noted that the Amendment states "claims 9-33 are cancelled", however, an amended claim 33 has been presented (see page 4).

Amended claims 1, 4-8, 33-36, 39 and 42-50 are pending in the application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claims 34, 45, 46, 48 and 50 are objected to because the phrases "wherein the heterologous gene is a cytokine" and "wherein the heterologous gene is an immunomodulator", "wherein the heterologous gene is a chemokine" are technically incorrect. This is because a gene is made up of nucleotide residues, whereas a cytokine or a chemokine or an immunomodulator is composed of amino acid residues. Thus, a gene can not be a cytokine or a chemokine or an immunomodulator. Examiner suggests that the term - - encodes - - should be used instead of the term "is". Appropriate correction is required.

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because all the

limitation in claim 4 (e.g., the heterologous gene replaces the S-gene and is expressed under control of endogenous S-promoter) is already present in claim 42 from which claim 4 is dependent upon.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, is withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 102

Amended claims 1, 4, 33, 39, 42-45 and 49 remain rejected under 35 U.S.C. 102(b) as being anticipated by Horwich et al. (WO 90/02176; IDS) for the same reasons already set forth in the previous Office Action.

Horwich et al. disclose the preparation of replication defective hepadnaviruses and in particular two types of defective hepadnavirus genomes, and the nucleic acid sequences thereof (see abstract and pages 15-18). Horwich et al. disclose the first type ("particle defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate cis-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. The second type of defective hepadnavirus genomes ("packaging genomes") produced pre-genomic RNA which can not be packaged and/or reverse-transcribed into a double-stranded genomic DNA, and produce messenger RNAs capable of supplying functions required *in trans* for packaging. Horwich et al.

further teach that hepadnavirus virion particles containing a particle-defective genome can be produced by coexpression of the particle-defective genome and "helper" hepadnavirus packaging genome(s). The resulting hepadnavirus containing a particle-defective genome can then be used for the infection of a hepatocyte, to which the particle-defective DNA is delivered and in which it can be expressed (page 16, second paragraph). Horwich et al. specifically teach to make permanent hepatic cell lines stably transfected with defective hepadnaviral genomes (packaging cell lines) that are capable of supplying necessary functions to defective hepadnaviral genomes and producing defective infectious particles (see page 18, first full paragraph). Horwich et al. teach the generation of several defective hepadnavirus genomes including those of hepatitis B virus pathogenic in humans, duck hepatitis B virus and others (see section 5.1.1 on page 29). Horwich et al. teach that their defective hepadnavirus virion particles containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or hepatic enzymes or a product which is toxic to a given pathogen that is the causative agent of a disorder affecting the liver (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45). Horwich et al. specifically teach that the heterologous gene sequence **replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression** (page 49, lines 1-5, and section 6.7 on page 69 for the exemplification showing the preparation of the S1 particle-defective genome by replacing the KpnI-XbaI fragment, 68 bp, located between

nucleotide positions 1290 and 1358, of the DHBV wild-type sequence with a synthetic linker of the same size). Horwich et al. further teach that specific initiation signals are also required for efficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation codon must be in phrase with the reading frame of the protein coding sequences to ensure the translation of the entire insert (see page 35, first full paragraph).

Therefore, the teachings of Horwich et al. meet every limitation of the instant claims. Accordingly, Horwich et al. anticipate the instant claims.

Response to Amendment

Applicants' arguments related to the above rejections in the Amendment filed on 6/16/03 in Paper No. 21 (pages 12-14) have been fully considered.

Applicants argue mainly that Horwich does not disclose nor teach that a heterologous gene sequence can replace the gene coding for the surface antigen. Rather, Horwich inserts a synthetic linker into the S-gene such that part of the S-gene sequences were replaced, and that the linker contains exactly the same nucleotide sequence as the replaced S-gene except for a three nucleotide exchange to knock out DHBV genes in order to generate "particle defective genomes". Applicants further argue that there is no showing that the system taught by Horwich produces defective particles at a titer level competent to infect hepatocytes nor has infectivity of any HBV particle produced been shown or proven.

Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, Horwich et al. teach clearly that **the heterologous gene sequence replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression** (page 49, lines 1-5), and that defective hepadnavirus virion particles containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or hepatic enzymes or a product which is toxic to a given pathogen that is the causative agent of a disorder affecting the liver (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45).

Secondly, the example using a synthetic linker is only one embodiment of the Horwich's teachings.

Thirdly, there is no requirement in the instant specification nor in the WO 90/02176 (Horwich's teachings) that an example for every taught embodiment has to be provided. At the filing date, an ordinary artisan in the art has a high level of skill for making recombinant hepadnaviruses through recombinant biology techniques as evidenced by some of the exemplifications taught by Horwich et al.

Accordingly, the instant claims remain rejected under 35 U.S.C. 102(b) as being anticipated by Horwich et al. (WO 90/02176; IDS) for the reasons stated above.

Claim Rejections - 35 USC § 103

Amended claims 33-36, 43, 46-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwich et al. (WO 90/02176; IDS) in view of Alber et al. (U.S. Patent No. 5,928,636) for the same reasons set forth in the previous Office Action.

Horwich et al. disclose the preparation of replication defective hepadnaviruses and in particular two types of defective hepadnavirus genomes, and the nucleic acid sequences thereof (see abstract and pages 15-18). Horwich et al. disclose the first type ("particle defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate cis-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. The second type of defective hepadnavirus genomes ("packaging genomes") produced pre-genomic RNA which can not be packaged and/or reverse-transcribed into a double-stranded genomic DNA, and produce messenger RNAs capable of supplying functions required *in trans* for packaging. Horwich et al. further teach that hepadnavirus virion particles containing a particle-defective genome can be produced by coexpression of the particle-defective genome and "helper" hepadnavirus packaging genome(s). The resulting hepadnavirus containing a particle-defective genome can then be used for the infection of a hepatocyte, to which the particle-defective DNA is delivered and in which it can be expressed (page 16, second paragraph). Horwich et al. specifically teach to make permanent hepatic cell lines stably transfected with defective hepadnaviral genomes (packaging cell lines) that are capable of supplying necessary functions to defective hepadnaviral genomes and producing defective infectious particles (see page 18, first full paragraph). Horwich et

al. teach the generation of several defective hepadnavirus genomes including those of hepatitis B virus pathogenic in humans, duck hepatitis B virus and others (see section 5.1.1 on page 29). Horwich et al. teach that their defective hepadnavirus virion particles containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or **hepatic enzymes or a product which is toxic to a given pathogen that is the causative agent of a disorder affecting the liver** (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45). Horwich et al. specifically teach that **the heterologous gene sequence replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression** (page 49, lines 1-5, and section 6.7 on page 69 for the exemplification showing the preparation of the S1 particle-defective genome by replacing the KpnI-XbaI fragment, 68 bp, located between nucleotide positions 1290 and 1358, of the DHBV wild-type sequence with a synthetic linker of the same size). Horwich et al. further teach that specific initiation signals are also required for efficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation codon must be in phrase with the reading frame of the protein coding sequences to ensure the translation of the entire insert (see page 35, first full paragraph).

Horwich et al. do not specifically teach the utilized heterologous gene encodes for a cytokine, a chemochine or any one of IFNalpha, IFNbeta, IFNgamma, TNFalpha, IL-18 or IL-12.

However, at the effective filing date of the present application, Alber et al. teach that IFNalpha has proven to be effective in the treatment of viral infections, e.g., both HBV and HCV infections (col. 2, lines 1-3). Alber et al. also teach that the combined use of IFNalpha and IL-12 is useful for treating chronic infectious viral diseases including hepatitis B, hepatitis C, HIV and others due to the synergistic interaction of IFNalpha and IL-12 (see abstract). Alber et al. also note that interferon cDNAs and IL-12 cDNA are available in the prior art, and therefore interferons and IL-12 can be produced recombinantly (see col. 1, lines 59-67; col. 4, lines 18-25).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the replication defective recombinant hepadnaviruses, and methods for expressing a heterologous gene in a hepatocyte, and for producing replication defective recombinant hepadnavirus particles taught by Horwich et al. by using a gene encoding IFNalpha or other interferons (e.g., IFNgamma) or IL-12 as the heterologous gene in light of the teachings of Alber et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification to produce recombinant interferons or IL-12 in a hepatocyte expression system because interferons and IL-12 are useful for treating chronic liver infectious diseases such as hepatitis B and hepatitis C. Alternatively, one of ordinary skilled artisan would have been motivated to carry out the above modification to investigate the effectiveness of the modified replication defective recombinant hepadnavirus particles expressing IFNalpha or IFNgamma or IL-12 in an animal model of chronic liver infectious diseases.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Amendment

Applicants' arguments related to the above rejections in the Amendment filed on 6/16/03 in Paper No. 21 (pages 15-17) have been fully considered.

Applicants argue mainly that Horwich does not show that a heterologous gene was inserted, and that Alber teaches away from the claimed invention because of the required co-expression system. Applicants further argue that Applicants neither intend to express any recombinant protein, nor is a recombinant protein systemically applied (as proposed by Alber), nor is it intended to or is IL-12 and IFNalpha co-express with the help of recombinant hepadnavirus genomes. Therefore, neither Horwich nor Alber, nor a combination thereof teaches or suggests the features of the presently claimed invention.

Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, Horwich et al. teach clearly that **the heterologous gene sequence replaces the gene coding for the surface antigen, and specifically that the recombinant hepadnavirus DNA can retain pre-S DNA sequences which contain promoters for surface antigen expression** (page 49, lines 1-5), and that defective hepadnavirus virion particles containing a heterologous gene sequence which encodes for an immunogenic epitope (an agent that modulates a host immune response) or

hepatic enzymes or **a pr duct which is toxic to a given path g n that is the causative agent of a disorder affecting the liver** (see section 5.1.3.1 on page 38, and section 5.2 on page 44, particularly first full paragraph on page 45). IFNα or other interferons (e.g., IFNγ) or IL-12 are products that are toxic to HBV and HBC which are causative agents of a disorder affecting the liver in light of the teachings of Aber et al.

Secondly, nowhere in the teachings of Aber et al. that examiner finds that the genes encoding for IFNα or other interferons or IL-2 have to be incorporated into the same recombinant vector, and therefore Aber et al. do not teach away or teach a non-enabled embodiment as alluded to by Applicants. It should be noted that recombinant IFNα or other interferons or IL-2 can be produced independently one from the others in culture.

Thirdly, the motivations for the combination of the references of Horwich et al. and Aber et al. in the above 103 rejection are not required to be the same as Applicants' intention in order to arrive at the presently claimed invention. This supports that the rejection was not made based on the teachings of the instant specification.

Accordingly, the instant claims remain rejected under 35 U.S.C. 103(a) as being unpatentable over Horwich et al. (WO 90/02176; IDS) in view of Alber et al. (U.S. Patent No. 5,928,636) for the reasons stated above.

Following is a new ground of rejection necessitated by Applicants' am ndment.

Claim Rejections - 35 USC § 112

Claims 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-8 are dependent on the cancelled claim 41. Therefore, the metes and bounds of the claims are not clearly determined because it is not clear what Applicants intend to claim.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER